In the Specification

Please substitute the following title of the invention on page 1:

~~COMPLETE BIOSYNTHETIC GENE SET FOR SYNTHESIS OF POLYKETIDE ANTIBIOTICS, INCLUDING THE ALBICIDIN FAMILY, RESISTANCE GENES, AND USES THEREOF~~

BIOSYNTHETIC GENES AND HOST CELLS FOR THE SYNTHESIS OF POLYKETIDE ANTIBIOTICS AND METHOD OF USE

Please substitute the following first paragraph on page 1:

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is the U.S. national stage application of International Patent Application No. PCT/US2003/33142, filed October 17, 2003, which claims the benefit of U.S. Provisional patent application with Serial No. 60/419,463, filed October 18, 2002 the ~~disclosure~~ disclosures of which ~~is~~ are hereby incorporated by reference in ~~its~~ their entirety, including all nucleic acid sequences, amino acid sequences, chemical formulae, tables and figures.

Please insert the following paragraph on page 1, before paragraph [0001]:

The Sequence Listing for this application is labeled "seq-list-replace.txt" which was created on June 26, 2008 and is 323 KB. The entire contents of the sequence listing is incorporated herein by reference in its entirety.

Please substitute paragraphs [0015], [0016], [0017] and [0018] beginning on page 4 as follows:

**Figure 5** is an illustration of the alignment of the primary sequences between the conserved motifs A4 and A5 of Alb NPRSs and PKS-4 in *Xanthomonas albilineans* with the corresponding sequences of GrsA (Phe) accession number: P14687 (SEQ ID NO: 132) and Blm NRPS-2 (β-Ala) accession number AF210249 (SEQ ID NO: 133); AlbI NRPS-1 (SEQ ID NO: 134); AlbI NRPS-3 (SEQ ID NO: 135); AlbIX NRPS-6 (SEQ ID NO: 136); AlbIX NRPS-7 (SEQ ID NO: 137); AlbIV

NRPS-5 (SEQ ID NO: 138); AlbVII PKS-4 (SEQ ID NO: 139); AlbI NRPS-2 (SEQ ID NO: 140).

**Figure 6** shows Rho-independent transcription terminators identified in the intergenic regions of XALB1 and XALB3 clusters (SEQ ID NO: 141, XALB1 Strand + (29 bp downstream from the TGA stop codon of *albXVII*); SEQ ID NO: 142, XALB1 Strand + (400 bp downstream from the TAA stop codon of *albIV*); SEQ ID NOs: 143, 144 and 145, XALB1 Strand – (62 bp, 170 bp and 560 bp downstream from the TAG stop codon of *albXVI*); SEQ ID NOs: 146 and 147, XLAB3 Strand+).

**Figure 7A** shows sequences identified as a putative bidirectional promoter between albX and albXVII in XALB1 for transcriptional control of operons 3 and 4 (SEQ ID NOs: 148 and 149).

**Figure 7B** shows sequences identified as a putative unidirectional promoter upstream from *albXIX* for transcriptional control of operon 5 if *albXVIII* is not expressed (SEQ ID NOs: 152 and 153).

Please substitute paragraphs [0022] and [0023] beginning on page 5 as follows:

**Figure 10A** is an alignment of the conserved motifs in AT domains from RifA-1 (SEQ ID NO: 156), -2 (SEQ ID NO: 157), -3 (SEQ ID NO: 158), RifB-1 (SEQ ID NO: 159), RifE-1 (SEQ ID NO: 160) (Rifamycin PKSs, August *et al.*, 1998) and BlmVIII (Bleomycin PKS; Du *et al.*, 2000) (SEQ ID NO: 161).

**Figure 10B** is a comparison of AlbXIII (SEQ ID NO: 162), FenF (a malonyl-CoA transacylase located upstream from *mycA*, Duitman *et al.*, 1999) (SEQ ID NO: 163) and LipA (a lipase; Valdez *et al.*, 1999) (SEQ ID NO: 164).

Please substitute paragraph [00120] beginning on page 35 as follows:

*albII* potentially encodes a protein of 343 aa (AlbII) with a predicted size of 37.7 kDa. *albII* is 100% identical to the *xabC* cistron, previously described as encoding an *O*-methyltransferase downstream *xabB* (Huang *et al.*, 2000a). This conclusion is based on the similarity of XabC with a family of methyltransferases that utilize S-adenosyl-L-methionine (SAM) as a co-substrate for *O*-methylation including TcmO protein from *Streptomyces glaucescens* (Huang *et al.*, 2000a). AlbII contains three highly conserved motifs of SAM-dependent methyltransferases, including the motif I

involved in SAM binding (Figure 3). In the Figure, identical or similar amino acids (A=G; D=E; I=L=V) are shown in bold. Numbers indicate the position of the amino acid from the N-terminus of the protein. Abbreviations used in the Figure are: Sgl-TcmO (SEQ ID NOs: 55, 56 and 57) and Sgl-TcmN (SEQ ID NOs: 58, 59 and 60), multifunctional cyclase-hydratase-3-*O*-Mtase and tetracenomycin polyketide synthesis 8-*O*-Mtase of *Streptomyces glaucescens*, respectively (accession number: M80674); Smy-MdmC, midecamycin-*O*-Mtase of *Streptomyces mycarofaciens* (accession number: M93958) (SEQ ID NOs: 61, 62 and 63); Mxa-SafC, Saframycin *O*-Mtase of *Myxococcus xanthus* (accession number: U24657) (SEQ ID NO:s: 64, 65 and 66); Ser-EryG, erythromycin biosynthesis *O*-Mtase of *Saccharopolyspora erythraea* (accession number: S18533) (SEQ ID NOs: 67, 68 and 69); Spe-DauK, carminomycin 4-O-Mtase of *Streptomyces peucetius* (accession number: L13453) (SEQ ID NOs: 70, 71 and 72); Sal-DmpM, *O*-demethylpuromycin-*O*-Mtase of *Streptomyces alboniger* (accession number: M74560) (SEQ ID NOs: 73, 74 and 75); Shy-RapM, rapamycin *O*-Mtase of *Streptomyces hygroscopicus* (accession number: X86780) (SEQ ID NOs: 76, 77 and 78); Sav-AveD, avermectin B 5-*O*-Mtase of *Streptomyces avermitilis* (accession number: G5921167) (SEQ ID NOs: 79, 80 and 81), Sar-Cmet, mithramycin *C*-methyltransferase of *Streptomyces argillaceus* (accession number: AF077869) (SEQ ID NOs: 82, 83 and 84); AlbII, putative albicidin biosynthesis *C*-Methyltransferase of *Xanthomonas albilineans* (SEQ ID No. 27); identical to XabC, accession number: AF239749) (SEQ ID NOs: 85, 86 and 87).

Please substitute paragraph [00122] beginning on page 35 as follows:

*albVI* potentially encodes a protein of 286 aa (AlbVI) with a predicted size of 32.1 kDa similar to several hypothetical protein from *Mycobacterium tuberculosis* (Genbank accessions No. AAK46042, AAK48238, AAK44517, AAK46218) and from *S. coelicolor* (Genbank accession No. CAC03631). AlbVI is also similar to the tetracenomycine C synthesis protein (TcmP) of *Pasteurella multocida* (Table 4). Four highly conserved motifs in TcmP and other *O*-methyltransferases are also present in AlbVI (Figure 4), suggesting that AlbVI is an *O*-methyltransferase. In the Figure, identical or similar aa (A=G; D=E; I=L=V; K=R) are shown in bold. Numbers indicate the position of aa from the N-terminus of the protein. Abbreviations used in the Figure are: Sgl-tcmP, tetracenomycin C synthesis protein of *Streptomyces glaucescens* (accession number: C47127) (SEQ ID NOs: 88, 89,

90 and 91); Sme-PKS, putative polyketide synthase of *Sinorhizobium meliloti* (accession number: AAK65734) (SEQ ID NOs: 92, 93, 94 and 95); Pmu-tcmP: tetracenomycin C synthesis protein of *Pasteurella multocida* (accession number: AAK03406) (SEQ ID NOs: 96, 97, 98 and 99); Mtu-Omt: putative *O*-methyltransferase of *Mycobacterium tuberculosis* (accession number: AAK45444) (SEQ ID NOs: 100, 101, 102 and 103); Mlo-Hp: hypothetical protein containing similarity to *O*-methyltransferase of *Mesorhizobium loti* (accession number: BAB50127) (SEQ ID NOs: 104, 105, 106 and 107); ~~Mtu-Hp1~~Mtu-Hp: hypothetical protein of *Mycobacterium tuberculosis* (accession number: AAK46042) (SEQ ID NOs: 108, 109, 110 and 111); Mtu-Hp2: hypothetical protein of *Mycobacterium tuberculosis* (accession number: AAK48238) (SEQ ID NOs: 112, 113, 114 and 115); Mtu-Hp3: hypothetical protein of *Mycobacterium tuberculosis* (accession number: AAK44517) (SEQ ID NOs: 116, 117, 118 and 119); Mtu-Hp4: hypothetical protein of *Mycobacterium tuberculosis* (accession number: AAK46218) (SEQ ID NOs: 120, 121, 122 and 123); Sco-Hp: hypothetical protein of *Streptomyces coelicolor* (accession number: CAC03631) (SEQ ID NOs: 124, 125, 126 and 127); AlbVI, putative albicidin biosynthesis *O*-Methyltransferase of *Xanthomonas albilineans* (this study) (SEQ ID NOs: 128, 129, 130 and 131).

Please replace pages 1-93 (Sequence Listing) submitted on April 25, 2005 in the subject application with new pages 1-180 submitted herewith.